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Impact of Cardiac Biomarkers or Echocardiography on the Management of Patients with Acute Non-Massive Pulmonary Embolism

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Contents

Summary

Background: Cardiac biomarkers or echocardiography for assessing right ventricular function are recommended to risk-stratify patients with acute non-massive pulmonary embolism (PE) but it remains unclear whether these tests affect the management and clinical outcomes in daily practice.

Methods and results: Overall, 587 patients with acute non-massive PE from 18 hospitals were enrolled in the Swiss Venous Thromboembolism Registry (SWIVTER) of whom 178 (30%) neither had a biomarker test nor an echocardiographic evaluation. Compared to the 409 (70%) patients with biomarkers or echocardiography of whom 210 (51%) had at least one positive test, patients without any testing were younger (61±18 vs. 67±16 years; $p<0.001$), more often outpatient at diagnosis (64% vs. 46%; $p<0.001$), had more often provoked PE (45% vs. 34%; $p=0.010$) and cancer (32% vs. 22%; $p=0.015$), and had less frequently main pulmonary artery embolism (26% vs. 37%, $p=0.009$) or an increased PE severity index (59% vs. 70%; $p=0.012$). The hospitalization rates were 80% without vs. 93% with testing ($p<0.001$); thrombolysis and/or embolectomy were performed in 2.8% vs. 4.9% ($p=0.29$), and the 30-day rates of mortality and PE recurrence were 7.4% vs. 3.2%, respectively ($p=0.031$). The predictive value of biomarker testing or echocardiography was lost (HR 0.62, 95%CI 0.27-1.39; $p=0.24$) when adjusted for other univariate predictors of mortality and recurrent PE, including cancer, chronic lung disease and bleeding complications.

Conclusions: Although more than two thirds of the PE patients underwent risk assessment with a biomarker test or an echocardiogram, such testing had little impact on management and clinical outcomes.

Introduction

Annually, pulmonary embolism (PE) accounts for more than 100’000 deaths in the United States (1) and 330’000 deaths in Europe (2), with right ventricular dysfunction as the most common cause of early mortality (3). In PE patients with preserved systemic pressure and without signs of cardiogenic shock, common clinical signs of right ventricular dysfunction include tachycardia, hypoxia, and distended jugular veins. The electrocardiogram may reveal signs of right ventricular strain, including right bundle branch block, the SI-QIII type, or inverted T-waves in the precordial leads (4). However, the assessment of right ventricular function is often unreliable based on the initial clinical evaluation. For the risk stratification of hemodynamically stable PE patients, current consensus guidelines of the European Society of Cardiology recommend routine assessment of right ventricular function by cardiac biomarkers and/or echocardiography (5).

Whereas patients with normal levels of cardiac biomarkers or with preserved right ventricular function on echocardiography have an excellent early prognosis (6-7), positive biomarker tests or right ventricular dysfunction are strong predictors of adverse clinical outcomes (8-11). In the Swiss Venous Thromboembolism Registry (SWIVTER), cardiac troponin testing provided incremental prognostic information on top of the initial clinical evaluation with the simplified Pulmonary Embolism Severity Index (sPESI) (12). Although the optimal management of hemodynamically stable PE patients with positive biomarker or echocardiographic test results has not yet been defined, identification of an increased risk may affect clinical decision making. This includes inpatient vs. outpatient treatment, monitoring in the intermediate or intensive care unit vs. transfer to a regular ward, or the administration of reperfusion therapy, including

thrombolysis, catheter intervention, or surgical embolectomy vs. treatment with anticoagulants alone (13).

In the absence of data from prospective management studies, we aimed to investigate the use of cardiac risk stratification and its impact on the medical management and the occurrence of adverse clinical outcomes in consecutive hemodynamically stable patients with acute PE.

Methods

Patients

Four Swiss academic and fourteen non-academic acute care hospitals representatively distributed over the country enrolled 644 consecutive patients with acute pulmonary embolism in the prospective SWIss Venous ThromboEmbolism Registry (SWIVTER) between January 2009 and May 2010. Inclusion criteria were age ≥18 years and objectively confirmed acute PE, and no exclusion criteria were given. Eligible patients were enrolled at the time of PE diagnosis during clinical inpatient or outpatient visits. PE diagnosis had to be objectively confirmed by contrast-enhanced chest computed tomography, ventilation perfusion scintigraphy, or conventional pulmonary angiography. We excluded 39 (6%) patients with massive PE, defined as systolic systemic pressure of less than 90 mm Hg, and 18 (3%) patients treated on an outpatient basis without follow-up data of whom one patient had an increased sPESI. For the present analysis, 587 (91%) PE patients were included. In accordance with local regulations, the study was approved by the local ethics committees of participating hospitals.

Data and definitions

Study individuals were grouped into patients with and without available cardiac risk stratification test results. Cardiac risk stratification was defined as the presence of a biomarker test result or an echocardiographic evaluation for right ventricular function within 24 hours of PE diagnosis, and cardiac risk stratification was considered absent if neither a biomarker test nor an echocardiographic evaluation within 24 hours of PE diagnosis were performed.

Accepted biomarker tests included conventional troponin I (Beckman Coulter TnI, cut-off 0.09 µg/l), conventional (Roche Elecsys cTnT, cut-off 0.1 µg/l) or highly-sensitive (Roche Elecsys cTnT-hs, cut-off 0.014 µg/l) troponin T, and B-type natriuretic peptide (BNP, Alere Triage BNP, cut-off 100 pg/ml). A positive biomarker test was defined as a biomarker level higher than the above mentioned assay thresholds.

There was no central adjudication of echocardiographic images in SWIVTER but right ventricular dysfunction on echocardiography was predefined and diagnosed from participating centres if at least one of the following signs was present: right ventricular (RV) dimension >30 mm in the parasternal long axis, right-to-left ventricular dimension ratio >0.9 in the apical four-chamber view, moderate or severe systolic right ventricular dysfunction, tricuspid systolic velocity >2.6 m/s, septal flattening, or paradoxical septal motion.

Non-massive PE was defined as systemic blood pressure of >90 mm Hg. Provoked PE was defined according to the guidelines of the American College of Chest Physicians as PE associated with surgery, hospitalization, immobilization for more than 3 days, estrogen therapy, pregnancy, or prolonged travel of more than 5 hours, all within 30 days prior to PE diagnosis (14). An increased simplified Pulmonary Embolism Severity Index (sPESI) was defined as presence of at

least one of the following criteria: age >80 years, systemic systolic pressure <100 mm Hg, heart rate >110 beats per minute, oxygen saturation < 90%, cancer, heart failure, and chronic lung disease (15).

A standardized electronic case report form was used for the collection of anonymous data on patient demographics, hospital status at the time of PE diagnosis, clinical presentation, thrombosis localization and risk factors, cardiac risk stratification test results, treatment, and 30-day clinical outcomes including mortality, symptomatic objectively confirmed recurrent PE and bleeding requiring medical attention. Overall, 499 (85%) patients had completed 30-day follow-up, 76 (13%) had follow-up data for a minimum of 15 days, and 12 (2%) for less than 15 days.

Statistical analysis

Continuous variables with a normal distribution were described as mean values with standard deviations (SD), continuous variables with a skewed distribution as median values with interquartile ranges (IQR), and discrete variables as frequencies and percentages. Group comparisons of continuous variables with a normal distribution were performed by *t*-test, continuous variables with a skewed distribution by a ranksum test, and discrete variables by the chi square or Fisher's exact test.

Univariate logistic regression analysis reporting odds ratios (OR) with 95% confidence intervals was conducted to identify clinical factors associated with cardiac risk stratification. Subsequently, multivariate logistic regression analysis was performed to identify independent clinical factors associated with cardiac risk stratification.

Univariate Cox regression analysis reporting hazard ratios (HR) with 95% confidence intervals (CI) was performed to explore clinical factors associated with the combined endpoint of mortality and recurrent PE at 30 days. Then, multivariate Cox regression analysis was conducted to investigate whether cardiac risk stratification independently predicts 30-day clinical outcome. For both multivariate analyses, univariate predictors with a p-value <0.05 were entered in the regression model, and a backward elimination procedure was used to stepwise discard variables without significance. All reported p-values are twotailed. Data were analyzed using STATA 10 software (STATACorp LP, College Station, Texas, USA).

Results

Patient characteristics

Cardiac biomarker or echocardiographic test results were available in 409 (70%) patients of whom 210 (51%) had positive cardiac biomarkers or right ventricular dysfunction on echocardiography, and 199 (49%) had negative cardiac biomarkers and no signs of right ventricular dysfunction on echocardiography (Figure 1).

In comparison to patients with cardiac risk stratification, the 178 (30%) patients without cardiac risk stratification were younger, more often outpatients at the time of PE diagnosis, and more frequently had provoked or cancer-associated PE (Table 1). Patients without cardiac risk stratification less frequently had hypoxia, tachycardia, syncope, embolism of the pulmonary main stem or the main pulmonary arteries, right heart strain on electrocardiography, and an increased sPESI as compared to patients with cardiac risk stratification. Syncope, heart rate ≥110

beats/min, and increasing age were independently associated with testing of cardiac risk; outpatient status at the time of PE diagnosis, cancer, and provoked PE were associated with its absence (Table 2).

Overall, 264 (45%) patients were treated in academic and 323 (55%) in non-academic centres. There was no difference in the use of cardiac risk stratification between academic vs. non-academic centres (69% vs. 70%; p=0.73). Among patients with cardiac risk stratification, a positive biomarker test or right ventricular dysfunction was more often present in patients from non-academic vs. academic centres (56% vs. 46%; p=0.038). There was no difference in the proportion of patients with an increased sPESI (65% vs. 69%; p=0.33) and with main stem or main pulmonary artery embolism (34% vs. 33%; p=0.78) between non-academic and academic centres.

Initial and long-term treatment of VTE

In comparison to patients with cardiac risk stratification, patients without cardiac risk stratification less often were treated on an inpatient basis and less frequently received systemic thrombolysis (Table 1). However, any reperfusion therapy, including systemic thrombolysis, catheter intervention or surgical embolectomy, was similarly often used in patients with and without cardiac risk stratification.

Among patients with cardiac risk stratification, the hospitalization rate was 98% in patients with at least one positive test result and 88% in patients without any positive test result (p<0.001), and there was more frequent use of reperfusion therapy in patients with at least one positive test result

(7% vs. 3%; p=0.030). Patients from academic centres were less often hospitalized (86% vs. 92%; p=0.010) but more frequently received reperfusion therapy than those from non-academic centres (7% vs. 2%; p=0.001).

Clinical outcomes at 30 days

The overall rate of cumulative 30-day mortality was 3.2%; 2.7% in patients with and 4.3% without cardiac risk stratification (p=0.35). The combined rate of 30-day mortality or recurrent PE was 4.4%; 3.2% in patients with and 7.4% without cardiac risk stratification (p=0.031) (Figure 2). The rate of 30-day bleeding requiring medical attention was 4.6%; 4.2% in patients with and 5.8% without cardiac risk stratification (p=0.72).

Among patients with cardiac risk stratification, the rate of cumulative 30-day mortality was 4.9% in patients with at least one positive test result and 0.5% in patients without any positive test (p=0.008). The overall combined rate of 30-day mortality or recurrent PE was 5.8% in patients with at least one positive test and 0.5% in patients without any positive test (p=0.003). The rate of 30-day bleeding requiring medical attention was 6.7% in patients with at least one positive test and 1.5% in patients without any positive test (p=0.009).

There was no significant difference in the combined rate of 30-day mortality or recurrent PE between academic vs. non-academic centres (5.9% vs. 3.2%; p=0.13).

Predictors of adverse clinical outcome

The strongest univariate factors associated with mortality or PE recurrence at 30 days were cancer, chronic lung disease, and bleeding requiring medical attention. Cardiac risk stratification was univariately associated with a 57% reduction in relative risk of mortality or PE recurrence (Table 3). Cardiac risk stratification lost its predictive value for mortality and recurrent PE when adjusted for the presence of cancer, chronic lung disease, and bleeding requiring medical attention.

Discussion

Although cardiac risk stratification was frequently performed in the Swiss Venous Thromboembolism Registry, with more than two thirds of PE patients receiving a biomarker test or an echocardiographic evaluation for assessing right ventricular function, such testing had only modest impact on clinical patient management. Cardiac risk stratification was associated with a higher proportion of inpatient treatment but it did not result in an increased use of reperfusion therapy as compared to patients without cardiac risk assessment. Only a minority of patients (7%) with positive test results received reperfusion therapy, proving that cardiac risk stratification test results were rarely used to guide management decisions. These findings may be explained by the fact that todate no convincing outcome data are available to support the use of reperfusion therapy for hemodynamically stable PE patients with biochemical or echocardiographic evidence of right ventricular dysfunction.

In the univariate analysis, patients without cardiac risk stratification had worse clinical outcomes than patients with cardiac risk stratification. However, such testing was not predictive of the combined endpoint of mortality and recurrent PE when adjusted for other important prognostic factors, such as cancer, chronic lung disease, or bleeding complications.

Without doubt, patients with and without cardiac risk stratification were not comparable. Patients without cardiac risk stratification were younger and more often outpatient at the time of diagnosis, and had clinically and anatomically less severe PE. In contrast, other patients without cardiac risk stratification had important comorbidities as reflected by a greater proportion of patients with an increased sPESI as compared to patients with cardiac risk stratification. Obviously, physicians abstained from ordering biomarker tests or echocardiography in two distinct risk scenarios: prognosis was likely estimated as being poor in the presence of cancer and other severe comorbidities regardless of PE severity, and it was estimated as being favourable in case of younger age or clinically less severe PE.

In our study, patient characteristics, comorbidities, and clinical findings were consistent with other studies on patients with acute non-massive PE (16-17). The proportion of patients with an increased sPESI in our study (66%) and in the validation study (69%) was similar (15). Overall, 90% of the patients were managed in-hospital in our study. However, this proportion will possibly decline in the future because outpatient management is feasible and safe according to a recent randomized trial on outpatient management of low-risk PE patients (18).

One strength of our study is the prospective enrolment of consecutive patients with acute non-massive PE and the systematic collection of information on biomarker test results, echocardiographic evaluation, management, and clinical outcomes. To the best of our knowledge,

SWIVTER is the first study to evaluate the use of cardiac risk stratification and its impact on management and outcomes in routine clinical practice. One study limitation is that not all patients had completed 30-day follow-up. Another limitation is that the reasons for withholding biomarker or echocardiographic testing were not documented. Since risk stratification was not randomized, the observed effect of cardiac risk stratification on clinical outcomes should be interpreted cautiously. However, because positive test results rarely affected clinical management decisions, we doubt that assignment of cardiac risk stratification within a randomized study would currently result in improved clinical outcomes. Although reperfusion therapy may be used more frequently in other countries, our findings challenge the guideline recommendations from the European Society of Cardiology (5) and the American Heart Association (13) for routinely obtaining cardiac risk stratification tests in hemodynamically stable PE patients. The large ongoing Pulmonary Embolism International Thrombolysis (PEITHO, ClinicalTrials.gov Identifier: NCT00639743) trial on patients with biochemical and imaging evidence of right ventricular dysfunction will help answering the question whether there is a place for routine cardiac risk stratification and for reperfusion therapy in this setting.

In summary, more than two thirds of the PE patients had a biomarker test or an echocardiographic evaluation. However, such testing did not result in an increased use of reperfusion treatment or improved clinical outcomes. Future research is warranted to clarify the role of routine cardiac risk stratification and the optimal management for hemodynamically stable patients with acute PE.

Table 1. Demographics, comorbidities, clinical findings, and VTE therapy

	Total **N = 587**	**Cardiac Risk Stratification** **N = 409**	**No Cardiac Risk Stratification** **N = 178**	**P**
Demographics				
Age, mean years ± SD	65 ± 16	67 ± 16	61 ± 18	<0.001
Age >80 years, n (%)	105 (17.9)	81 (19.8)	24 (13.5)	0.07
Women, n (%)	273 (46.5)	198 (48.4)	75 (42.1)	0.16
Inpatient at the time of diagnosis, n (%)	301 (48.7)	188 (54.0)	113 (36.5)	<0.001
Comorbidities				
Cancer, n (%)	149 (25.4)	92 (22.5)	57 (32.0)	0.015
Prior thromboembolism, n (%)	143 (24.4)	98 (24.0)	45 (25.3)	0.73
Bed rest for >3 days within 30 days, n (%)	99 (16.9)	60 (14.7)	39 (21.9)	0.031
Chronic lung disease, n (%)	85 (14.5)	53 (13.0)	32 (18.0)	0.11
Obesity, n (%)	84 (14.3)	64 (15.7)	20 (11.2)	0.16
Surgery within 30 days, n (%)	74 (12.6)	49 (12.0)	25 (14.0)	0.49
Acute respiratory failure, n (%)	47 (8.0)	35 (8.6)	12 (6.7)	0.46
Congestive heart failure, n (%)	45 (7.7)	36 (8.8)	9 (5.1)	0.12
Ongoing chemotherapy, n (%)	41 (7.0)	23 (5.6)	18 (10.1)	0.050
Bleeding requiring medical attention, n (%)	29 (4.9)	17 (4.2)	12 (6.7)	0.18
Thrombocytopenia, n (%)	17 (2.9)	9 (2.2)	8 (4.5)	0.13
Clinical findings				
Dyspnea, n (%)	483/584 (82.7)	351/408 (86.0)	132/176 (75.0)	0.001
Right heart strain on ECG, n (%)	204/448 (45.5)	177/363 (48.8)	27/85 (31.8)	0.005
Provoked PE, n (%)	218 (37.1)	138 (33.7)	80 (44.9)	0.010
Thrombosis of main stem or main pulmonary arteries, n (%)	197 (33.6)	151 (36.9)	46 (25.8)	0.009
Oxygen saturation in room air <90%, n (%)	146/526 (27.8)	112/364 (30.8)	34/162 (21.0)	0.021
Heart rate ≥110 beats/min, n (%)	130/563 (23.1)	107/396 (27.0)	23/167 (13.8)	0.001
Syncope, n (%)	44/584 (7.5)	40/408 (9.8)	4/176 (2.3)	0.002
Increased sPESI, n (%)	390 (66.4)	285 (69.7)	105 (59.0)	0.012
Therapy				
Inpatient therapy, n (%)	524 (89.3)	381 (93.2)	143 (80.3)	<0.001
Reperfusion therapy*, n (%)	25 (4.3)	20 (4.9)	5 (2.8)	0.25
Systemic thrombolysis, n (%)	13 (2.2)	13 (3.2)	0 (0.0)	0.016
Catheter therapy, n (%)	8 (1.4)	6 (1.5)	2 (1.1)	0.74
Surgical thrombectomy, n (%)	7 (1.2)	4 (1.0)	3 (1.7)	0.47
Inferior vena cava filter, n (%)	14 (2.4)	10 (2.4)	4 (2.3)	0.89
Planned duration of anticoagulation				
<=3 months, n (%)	38 (6.5)	23 (5.6)	15 (8.4)	0.20
>3-12 months, n (%)	374 (63.7)	259 (63.3)	115 (64.6)	0.77
>12 months or indefinite, n (%)	175 (29.8)	127 (31.1)	48 (27.0)	0.32

*some patients had a combination of systemic thrombolysis, catheter therapy, or surgical thrombectomy; sPESI simplified Pulmonary Embolism Severity Index;

Table 2. Clinical factors associated with absent testing of cardiac risk (N=560)

Analysis	**Univariate**			**Multivariate**		
Factor	**OR**	**95% CI**	**P**	**OR**	**95% CI**	**P**
Outpatient at the time of PE diagnosis	2.04	1.42-2.93	<0.001	2.24	1.49-3.36	<0.001
Cancer	1.62	1.10-2.40	0.015	1.81	1.17-2.79	0.008
Provoked PE	1.60	1.11-2.30	0.010	1.58	1.05-2.40	0.029
Age, per year	0.98	0.97-0.99	<0.001	0.98	0.97-0.99	<0.001
Heart rate ≥110 beats/min	0.43	0.26-0.71	0.001	0.43	0.26-0.73	0.002
Syncope	0.21	0.08-0.61	0.004	0.29	0.10-0.83	0.022

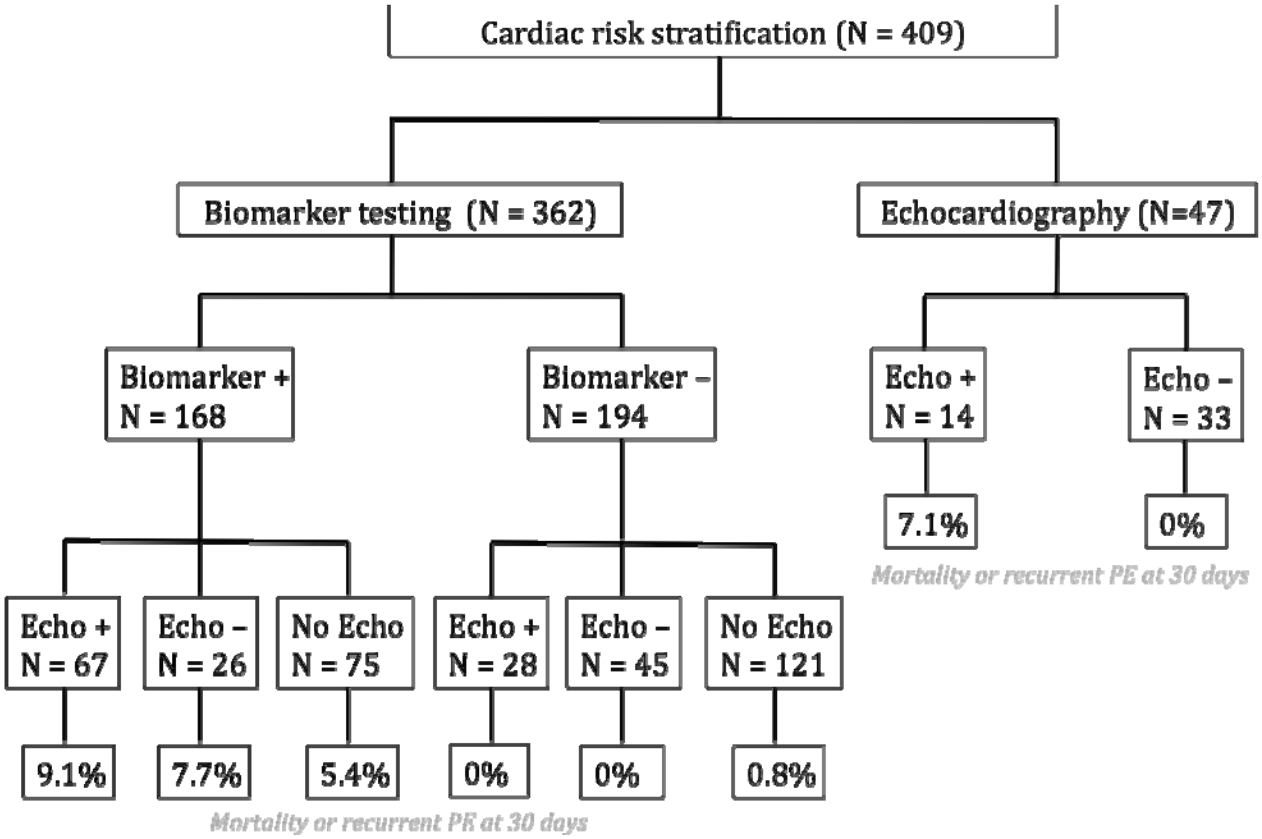
OR odds ratio; CI confidence interval; PE pulmonary embolism

Table 3. Clinical factors associated with combined mortality and recurrent pulmonary embolism at 30 days

Analysis	**Univariate**			**Multivariate**		
Factor	**HR**	**95% CI**	**P**	**HR**	**95% CI**	**P**
Cancer	4.43	1.99-9.87	<0.001	3.75	1.65-8.52	0.002
Bleeding requiring medical attention	3.82	1.31-11.14	0.014	3.62	1.23-10.66	0.020
Chronic lung disease	2.77	1.19-6.41	0.018	2.25	0.95-5.33	0.064
Cardiac risk stratification (biomarkers or echocardiography)	0.43	0.20-0.95	0.036	0.62	0.27-1.39	0.24

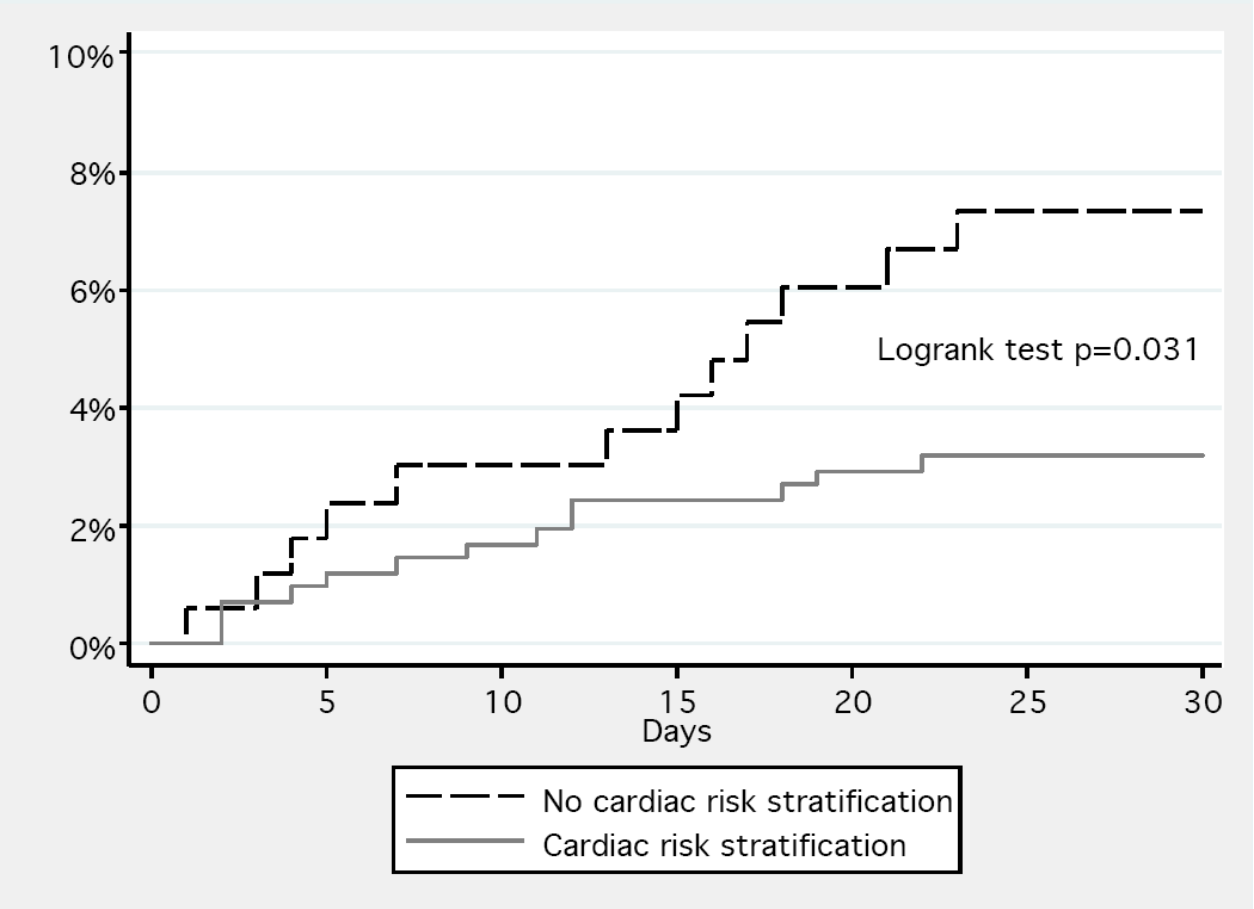
HR hazard ratio; CI confidence interval

Figure 1. Biomarker testing and echocardiographic results with rates of combined mortality and recurrent pulmonary embolism at 30 days



Echo +: right ventricular dysfunction on echocardiography; Echo –: no right ventricular dysfunction on echocardiography; No Echo: echocardiography not available

Figure 2. Unadjusted rates of the combined endpoint of mortality and recurrent pulmonary embolism through 30 days



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